

FORM PTO-1390 (REV. 11-2000)		U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
				Le A 33 783
		U.S. APPLICATION NO (If known, see 37 CFR 1.5)		10/018927
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				
INTERNATIONAL APPLICATION NO. PCT/EP00/05564	INTERNATIONAL FILING DATE 16 June 2000 (16.06.00)	PRIORITY DATE CLAIMED 29 June 1999 (29.06.99)		
TITLE OF INVENTION 6-CARBOXYPHENYLDIHYDROPIRIDAZINONE DERIVATIVES AND USE THEREOF				
APPLICANT(S) FOR DO/EO/US STOLTEFUSS, et al.				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</p> <p>4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <ul style="list-style-type: none"> a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). <p>6. <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <ul style="list-style-type: none"> a. <input checked="" type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <ul style="list-style-type: none"> a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>				
Items 11 to 20 below concern document(s) or information included:				
<p>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input type="checkbox"/> A FIRST preliminary amendment.</p> <p>14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input checked="" type="checkbox"/> Other items or information: 1) Certificate of Mailing under 37 C.F.R. 1.10; 2) Transmittal of Information Disclosure Statement under 37 C.F.R. 1.97(b); 3) Information Disclosure Citation (Modified Form PTO-1449) and references cited therein 4) Return Receipt Postcard.</p>				
Date of Deposit: DEC 2 1 2001 Express Mail Label No.: ET386113243US				

U.S. APPLICATION NO. (if known) 37 CFR 1.51 10/018927		INTERNATIONAL APPLICATION NO PCT/EP00/05564	ATTORNEY'S DOCKET NUMBER Le A 33 783																				
<p>21. <input checked="" type="checkbox"/> The following fees are submitted:</p> <p>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</p> <p>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$890.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00</p>		CALCULATIONS PTO USE ONLY																					
ENTER APPROPRIATE BASIC FEE AMOUNT =		\$ 890.00																					
<p>Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).</p>		\$																					
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>CLAIMS</th> <th>NUMBER FILED</th> <th>NUMBER EXTRA</th> <th>RATE</th> <th>\$</th> </tr> </thead> <tbody> <tr> <td>Total claims</td> <td>29 - 20 =</td> <td>9</td> <td>x \$18.00</td> <td>\$ 162.00</td> </tr> <tr> <td>Independent claims</td> <td>5 - 3 =</td> <td>2</td> <td>x \$80.00</td> <td>\$ 168.00</td> </tr> <tr> <td>MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td>1</td> <td></td> <td>+ \$270.00</td> <td>\$ 280.00</td> </tr> </tbody> </table>		CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	Total claims	29 - 20 =	9	x \$18.00	\$ 162.00	Independent claims	5 - 3 =	2	x \$80.00	\$ 168.00	MULTIPLE DEPENDENT CLAIM(S) (if applicable)	1		+ \$270.00	\$ 280.00	TOTAL OF ABOVE CALCULATIONS = \$ 1,500.00	
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MULTIPLE DEPENDENT CLAIM(S) (if applicable)	1		+ \$270.00	\$ 280.00																			
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +		\$																					
SUBTOTAL =		\$ 1,500.00																					
<p>Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).</p>		\$																					
TOTAL NATIONAL FEE =		\$ 1,500.00																					
<p>Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +</p>		\$																					
TOTAL FEES ENCLOSED =		\$ 1,500.00																					
		Amount to be refunded:	\$																				
		charged:	\$																				
<p>a. <input type="checkbox"/> A check in the amount of \$ _____ to cover the above fees is enclosed.</p> <p>b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>13-3372</u> in the amount of \$ <u>1,500.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>13-3372</u>. A duplicate copy of this sheet is enclosed.</p> <p>d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.</p>																							
<p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.</p>																							
<p>SEND ALL CORRESPONDENCE TO:</p> <p>Jeffrey M. Greenman Vice President, Patents and Licensing Bayer Corporation 400 Morgan Lane West Haven, CT 06516</p>																							
<p><i>William F. Gray</i></p>																							
<p>SIGNATURE</p>																							
<p>William F. Gray</p>																							
<p>NAME</p>																							
<p>31,018</p>																							
<p>REGISTRATION NUMBER</p>																							

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6-Carboxyphenyldihydropyridazinone derivatives and their use

The present invention relates to the field of erythropoiesis. In particular, the present invention relates to novel 6-carboxyphenyldihydropyridazinone derivatives, to processes for preparing them and to their use as medicaments, preferably for the prophylaxis and/or control of anemias.

Anemias are characterized by the erythrocyte count, hemoglobin concentration and/or hematocrit decreasing below the age-related and sex-specific reference values.

- 10 However, a decrease in one of these parameters is only a sign of an anemia when the blood volume is normal but not when the decrease is associated with acute, relatively marked blood losses, exsiccosis (pseudopolyglobulism) or hydremia (pseudoanemia). (Pschyrembel, Klinisches Wörterbuch Clinical Dictionary, 257th edition, 1994, Walter de Gruyter Verlag, page 59 ff., entry "Anemia"; Römpf Lexikon Chemie 15 [Römpf Chemistry Encyclopedia], version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Anemia").

As a consequence of the decreased capacity of the blood to transport oxygen, anemia is characterized clinically by, inter alia, disturbances in oxygen-dependent metabolism and organ functions; when the anemia develops acutely, for example as a consequence of the loss of blood, shock symptoms can appear, and, when it develops chronically, there is frequently a slowly progressing course associated with decline in performance, tiredness, dyspnea and tachycardia.

- 25 The different forms of anemia can be subdivided or classified either in accordance with the morphology and hemoglobin content of the erythrocytes or in accordance with etiology (for example into posthemorrhagic anemia, pregnancy anemia, tumor anemia, infection anemia and deficiency anemias). It is furthermore possible to subdivide the different forms of anemia in accordance with their pathogenesis while 30 taking into consideration the causes which are in principle possible, for example into anemias caused by excessive loss of blood (for example acute or chronic hemorrhagic anemia), anemias resulting from reduced or ineffective erythropoiesis

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(for example iron deficiency anemias, nephrogenic anemias or myelopathic anemias) and anemias resulting from excessive erythrocyte breakdown (what are termed hemolytic anemias) (Pschyrembel, Klinisches Wörterbuch, 257th edition, 1994, Walter de Gruyter Verlag, page 59 ff., entry "anemia"; Roche-Lexikon Medizin [Roche Medical Encyclopedia], 4th edition, 1999, Urban & Schwarzenberg, entry "anemia").

In practice, the methods for treating anemias which are disclosed in the prior art prove to be very difficult and not particularly efficient. Large numbers of side-effects, which are frequently serious to the patient, usually occur.

Thus, in the therapy of iron deficiency anemias, use is generally made of iron preparations which are administered either orally or parenterally. When they are administered orally, it is, in particular, gastrointestinal disturbances which are observed as side-effects. The simultaneous administration of antacids, for the purpose of treating the gastrointestinal disturbances, impairs absorption of the iron. Furthermore, the absorption of iron from the intestinal tract is in any case only very limited because of the ability of the mucosa to impede the passage of iron. On the other hand, a dose which is administered orally should not be too high because, if it is, symptoms of poisoning can then occur, in the worst case even a hemorrhagic gastroenteritis which is associated with shock symptoms and leads to death. Administration of the iron therapy parenterally, which likewise proves to be difficult because of the plasma only having a low ability to bind iron, can lead, particularly when an overdose is given, to nausea, vomiting, cardialgias and headaches, heat sensations and a severe fall in blood pressure associated with collapse, and, furthermore, to the deposition of iron in the reticuloendothelium (hemosiderosis); the blood vessel walls are damaged by the intravenous injection and thrombophlebitis and clot formation must be expected. Dosing proves to be extremely difficult since all the iron which cannot be bound physiologically when it is administered parenterally then has a toxic effect (Gustav Kuschinsky, Heinz Lüllmann and Thies Peters, Kurzes Lehrbuch der Pharmakologie und Toxikologie [Short Textbook of Pharmacology and Toxicology], 9th edition, 1981, Georg Thieme Verlag Stuttgart,

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pages 139 ff.; Ernst Mutschler, Arzneimittelwirkungen, Lehrbuch der Pharmakologie und Toxikologie [Effects of Pharmaceuticals, Textbook of Pharmacology and Toxicology], Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1986, pages 383 ff.).

5

For somewhat more than 10 years now, recombinant erythropoietin (rhEPO), which is prepared by genetic manipulation, has been available for therapeutic employment for treating severe anemias. This is because, it is known that recombinant human (rh) EPO stimulates erythropoiesis humorally, as a result of which it has come to be used
10 as an antianemic agent in the therapy of severe anemias, particularly in renal and nephrogenic anemias. In addition, rh EPO is used for increasing the number of endogenous blood cells in order to decrease the requirement for transfusions of foreign blood.

Erythropoietin (EPO) is a glycoprotein which has a molecular weight of about
15 34 000 Da. More than 90% of the EPO is synthesized in the kidney, and the EPO which is produced in this organ is secreted into the blood. The primary physiological function of EPO is that of regulating erythropoiesis in the bone marrow. In this location, EPO stimulates the proliferation and maturation of the erythrocytic precursor cells.

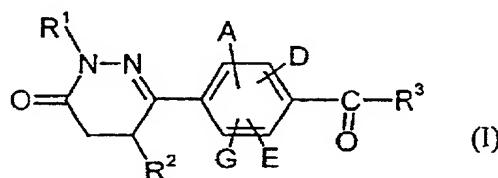
20 However, powerful side-effects occur when rh EPO is administered. These side effects include the development and amplification of high blood pressure and the causation of an encephalopathy-like symptomatology, leading all the way to tonic/clonic convulsions and cerebral or myocardial infarction due to thromboses. Furthermore, rh EPO is not available orally and has therefore to be administered
25 intraperitoneally (i.p.), intravenously (i.v.) or subcutaneously (s.c.), thereby restricting its use to the therapy of severe anemias (Kai-Uwe Eckardt, "Erythropoietin: Karriere eines Hormons" [Career of a Hormone], Deutsches Ärzteblatt 95, issue 6 dated February 6, 1998 (41), pages A-285 to A-290; Rote Liste [Red List] 1998, Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH,
30 see "Epoetin alpha" and "Epoetin beta").

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The object of the present invention is now to provide novel substances which are particularly suitable for treating anemias more efficiently and which, in this connection, avoid the disadvantages of the methods for treating anemias which are known from the prior art.

5

The present invention consequently relates to 6-carboxyphenyldihydropyridazinone derivatives of the general formula (I)



10

in which

A, D, E and G are identical or different and

represent hydrogen, halogen, trifluoromethyl or hydroxyl, or represent

15

(C₁-C₆)-alkyl or represent (C₁-C₆)-alkoxy,

R¹ and R² are identical or different and

represent hydrogen or represent (C₁-C₆)-alkyl,

20 R³

represents radicals of the formulae -OR⁴ or -NR⁵R⁶,

in which

25 R⁴ denotes cycloalkyl having from 3 to 8 carbon atoms or

(C₁-C₈)-alkyl which is optionally substituted by hydroxyl, (C₁-C₆)-alkoxy, cycloalkyl having from 3 to 8 carbon atoms or aryl having from 6 to 10 carbon atoms which, for its part, can be substituted, once to twice, identically or differently, by substituents which are selected

- 5 -

from the group: halogen, (C₁-C₆)-alkoxy, hydroxyl or trifluoromethyl,
or

denotes (C₁-C₈)-alkyl which is optionally substituted by a group of the
formula -NR⁷R⁸,

5

in which

R⁷ and R⁸ are identical or different and denote hydrogen, (C₁-C₆)-
alkyl or benzyl,

10

or

R⁴ denotes vinyl or allyl,

15

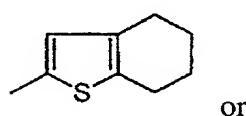
or

R⁴ denotes aryl having from 6 to 10 carbon atoms which is optionally
substituted, once to twice, identically or differently, by substituents
which are selected from the group consisting of: halogen, (C₁-C₆)-
alkyl, (C₁-C₆)-alkoxy or hydroxyl,

20

R⁵ denotes hydrogen or (C₁-C₄)-alkyl,

R⁶ denotes cycloalkyl having from 3 to 8 carbon atoms or a radical of the
25 formula



or

aryl having from 6 to 10 carbon atoms or a 5- to 7-membered
aromatic heterocycle having up to 3 heteroatoms from the series S, N
and/or O, it being possible for the ring systems which are listed here
to be optionally substituted, once to several times, identically or

30

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differently, by substituents which are selected from the group: halogen, trifluoromethyl, hydroxyl, (C₁-C₆)-alkoxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkyl and radicals of the formulae -SO₂-NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

5

in which

R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or (C₁-C₆)-alkyl,

10

and

a denotes a number 0 or 1,

15

or

20

R⁶ denotes (C₁-C₈)-alkyl which is optionally substituted, once to twice, identically or differently, by substituents which are selected from the group: halogen, trifluoromethyl, hydroxyl, (C₁-C₆)-alkoxy, carboxyl, (C₁-C₆)-alkoxycarbonyl and aryl having from 6 to 10 carbon atoms and from 5- to 7-membered aromatic heterocycles having up to 3 heteroatoms from the series S, N and/or O,

25
in which the ring systems can be optionally substituted, once to three times, identically or differently, by (C₁-C₆)-alkyl, halogen, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, trifluoromethyl or by the radical -CO-NH₂,

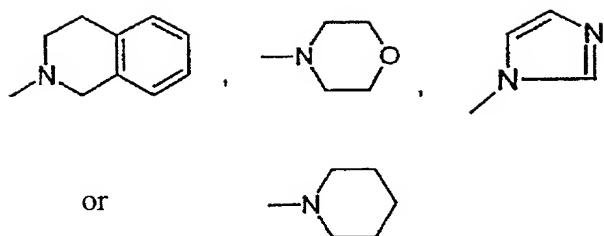
25

or

30

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae

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which, for their part, can be optionally substituted,

5 and the salts thereof,

with the exception, however, of the compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide.

10 The abovementioned compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide is disclosed in the publications Chem. Abstr. 77, 19664 and DE 21 50 436 (1972).

15 Depending on the substitution pattern, the compounds according to the invention can exist in stereoisomeric forms which either relate to each other as image and mirror image (enantiomers) or which do not relate to each other as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and to their respective mixtures. The racemic forms, like the diastereomers, can be resolved, in a known manner, into the stereoisomerically uniform constituents.

20

Physiologically harmless salts of the compounds according to the invention can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulfonic acids. Particular preference is given, for example, to salts with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalene-disulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

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Salts which may be mentioned are also salts with customary bases, for example alkali metal salts (e.g. sodium or potassium salts), alkaline earth metal salts (e.g. calcium or magnesium salts) or ammonium salts derived from ammonia or organic amines such as diethylamine, triethylamine, ethyl diisopropylamine, procaine,
5 dibenzylamine, N-methylmorpholine, dihydroabietylamine, 1-ephedrine or methyl-piperidine.

(C₃-C₈)-Cycloalkyl represents cyclopropyl, cyclopentyl, cyclobutyl, cyclohexyl, cycloheptyl or cyclooctyl. Cyclopropyl, cyclopentyl and cyclohexyl may be
10 mentioned as being preferred.

(C₆-C₁₀)-Aryl represents an aromatic radical having from 6 to 10 carbon atoms. Preferred aryl radicals are phenyl and naphthyl.

15 (C₁-C₆)-Alkyl represents a straight-chain or branched alkyl radical having from 1 to 6 carbon atoms. Examples which may be mentioned are: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl and n-hexyl. A straight-chain or branched alkyl radical having from 1 to 4 carbon atoms is preferred. A straight-chain or branched alkyl radical having from 1 to 3 carbon atoms is particularly preferred.
20

(C₁-C₆)-Alkoxy represents a straight-chain or branched alkoxy radical having from 1 to 6 carbon atoms. Examples which may be mentioned are: methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy and n-hexoxy. A straight-chain or branched alkoxy radical having from 1 to 4 carbon atoms is preferred. A straight-chain or branched alkoxy radical having from 1 to 3 carbon atoms is particularly preferred.
25

(C₁-C₆)-Alkoxycarbonyl represents a straight-chain or branched alkoxycarbonyl radical having from 1 to 6 carbon atoms. Examples which may be mentioned are:
30 methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl and tert-butoxycarbonyl. A straight-chain or branched alkoxycarbonyl radical having from 1 to 4 carbon atoms is preferred. A

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straight-chain or branched alkoxy carbonyl radical having from 1 to 3 carbon atoms is particularly preferred.

A 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the series

5 S, O and/or N represents, for example, pyridyl, pyrimidyl, pyridazinyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl or imidazolyl. Pyridyl, thienyl, pyridazinyl, furyl and thiazolyl are preferred.

Preference is given to compounds of the general formula (I) according to the
10 invention

in which

A, D, E and G are identical or different and

15 represent hydrogen, fluorine, chlorine, bromine or trifluoromethyl,

R¹ and R² are identical or different and

represent hydrogen or represent methyl,

20 R³ represents radicals of the formulae -OR⁴ or -NR⁵R⁶,

in which

R⁴ denotes cyclopropyl, cyclopentyl or cyclohexyl or

25 denotes (C₁-C₆)-alkyl which is optionally substituted by hydroxyl, (C₁-C₄)-alkoxy, cyclopropyl, cyclopentyl, cyclohexyl or phenyl which, for its part, can be substituted once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, (C₁-C₄)-alkoxy, hydroxyl or trifluoromethyl,

30 or

denotes (C₁-C₆)-alkyl which is optionally substituted by a group of the formula -NR⁷R⁸,

- 10 -

in which

R⁷ and R⁸ are identical or different and denote hydrogen or (C₁-C₄)-
5 alkyl,

or

R⁴ denotes allyl,

10

R⁵ denotes hydrogen or (C₁-C₃)-alkyl,

15

R⁶ denotes cyclopropyl, cyclopentyl or cyclohexyl or
denotes phenyl, thienyl, thiazolyl, furyl or pyridyl, it being possible
for the listed aromatic ring systems to be optionally substituted, once
to twice, identically or differently, by substituents selected from the
group: fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, (C₁-C₃)-
alkoxy, (C₁-C₃)-alkoxycarbonyl, (C₁-C₄)-alkyl and radicals of the
formulae -SO₂NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

20

in which

R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or
(C₁-C₄)-alkyl,

25

and

a denotes a number 0 or 1,

30

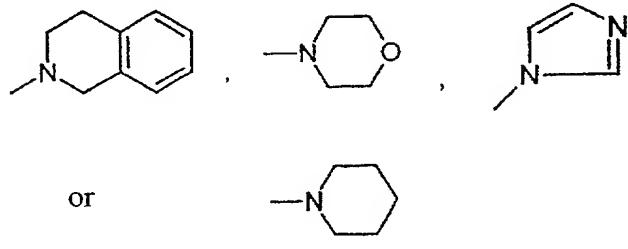
or

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R⁶ denotes (C₁-C₆)-alkyl which are optionally substituted once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkoxycarbonyl, phenyl, pyridyl, naphthyl, furyl or thiazolyl, it being possible for the ring systems to be optionally substituted, once to twice, identically or differently, by fluorine, chlorine, methyl, methoxycarbonyl, trifluoromethyl or by a radical of the formula -CO-NH₂,

10 or

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae



15

and the salts thereof,

with the exception, however, of the compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide.

Particular preference is given to compounds of the general formula (I) according to the invention

25 in which

A, D, E and G represent hydrogen,

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R¹ and R² are identical or different and
represent hydrogen or represent methyl,

5 R³ represents radicals of the formulae -OR⁴ or -NR⁵R⁶,

in which

10 R⁴ denotes cyclopropyl, cyclopentyl or cyclohexyl or
denotes (C₁-C₅)-alkyl which is optionally substituted by (C₁-C₄)-
alkoxy, cyclopropyl, cyclopentyl, cyclohexyl or phenyl which, for its
part, can be substituted, once to twice, identically or differently, by
substituents selected from the group: fluorine, chlorine, (C₁-C₄)-
alkoxy, hydroxyl or trifluoromethyl, or
15 denotes (C₁-C₄)-alkyl which is optionally substituted by a group of the
formula -NR⁷R⁸,

in which

20 R⁷ and R⁸ are identical or different and denote hydrogen, benzyl or
methyl,

or

25 R⁴ denotes allyl,

R⁵ denotes hydrogen or (C₁-C₃)-alkyl,

30 R⁶ denotes cyclopropyl, cyclopentyl or cyclohexyl or
denotes phenyl, naphthyl, thienyl, thiazolyl, furyl or pyridyl, with the
listed ring systems being optionally substituted once to twice,
identically or differently, by substituents selected from the group:

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fluorine, chlorine, bromine, trifluoromethyl, (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl, (C₁-C₃)-alkyl and radicals of the formulae -SO₂-NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

5

in which

R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or (C₁-C₄)-alkyl,

10

and

a denotes a number 0 or 1,

or

15

R⁶ denotes (C₁-C₆)-alkyl which is optionally substituted by substituents selected from the group: fluorine, chlorine, trifluoromethyl, (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl, phenyl, pyridyl, naphthyl, furyl, thienyl or thiazolyl, the ring systems optionally being substituted once to twice, identically or differently, by fluorine, chlorine, methyl, methoxycarbonyl or trifluoromethyl or by a radical of the formula -CO-NH₂,

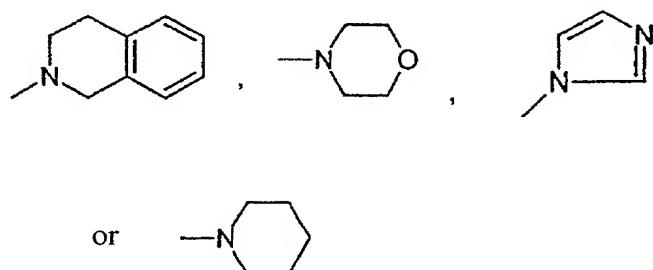
20

or

25

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae

- 14 -



and the salts thereof,

5

with the exception, however, of the compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide.

Very particular preference is given to compounds of the general formula (I)

10 according to the invention

in which

A, D, E and G represent hydrogen,

15

R³ represents the radical -NR⁵R⁶, where R⁵ = H or methyl and R⁶ is as previously defined,

and the remaining radicals have the previously mentioned meaning.

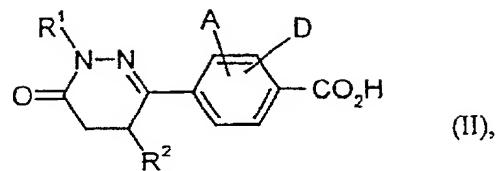
20

The present invention also relates to processes for preparing the compounds of the general formula (I) according to the invention, where

[A] in the case where R³ represents the radical of the formula -OR⁴ in the above
25 general formula (I),

compounds of the general formula (II)

- 15 -

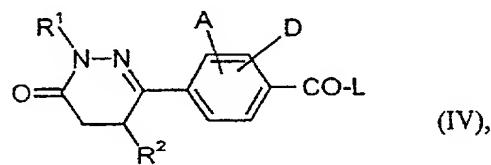


in which

- 5 A, D, R¹ and R² have the abovementioned meaning,

are initially converted, by reaction with carboxylic acid-activating reagents, such as thionyl chloride or carbonyldiimidazole and using customary methods, into the compounds of the general formula (IV)

10



in which

- 15 A, D, R¹ and R² have the abovementioned meaning,

and

20 L represents an activating radical, preferably chlorine or imidazolyl,

and, in a second step, compounds are reacted with compounds of the general formula (III)



25

- 16 -

in which

R⁴ has the abovementioned meaning,

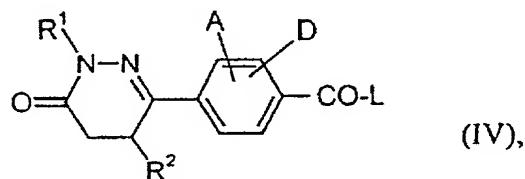
5 in inert solvents, where appropriate in the presence of a base,

or

[B] in the case where R³ represents the radical of the formula -NR⁵R⁶ in the
10 above general formula (I),

compounds of the general formula (II) are initially converted, by reaction with carboxylic acid-activating reagents, such as thionyl chloride or carbonyldiimidazole, and using customary methods, into the compounds of the general formula (IV)

15



in which

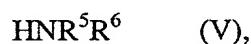
20 A, D, R¹ and R² have the abovementioned meaning,

and

L represents an activating radical, preferably chlorine or imidazolyl,

25

and, in a second step, reacted with amides of the general formula (V)



in which

R⁵ and R⁶ have the abovementioned meaning,

5

in inert solvents.

Within the meaning of the present invention, suitable carboxylic acid-activating reagents are, in particular, carbodiimides, such as diisopropylcarbodiimide, dicyclo-

10 hexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulfonate, or propane-phosphoric acid anhydride or isobutyl chloroformate or benzotriazolyloxytris-(dimethylamino)phosphonium hexyfluorophosphate or diphenyl phosphonate amide

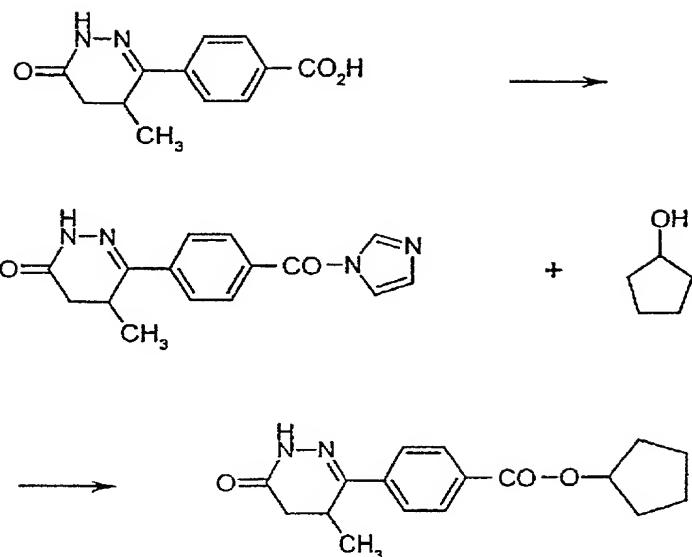
15 or methanesulfonyl chloride, where appropriate in the presence of bases such as triethylamine or N-ethylmorpholine or N-methylpiperidine or dicyclohexylcarbodiimide and N-hydroxysuccinimide. Thionyl chloride is also suitable. Preferred carboxylic acid-activating reagents are carbonyldiimidazole (CDI) and thionyl chloride.

20

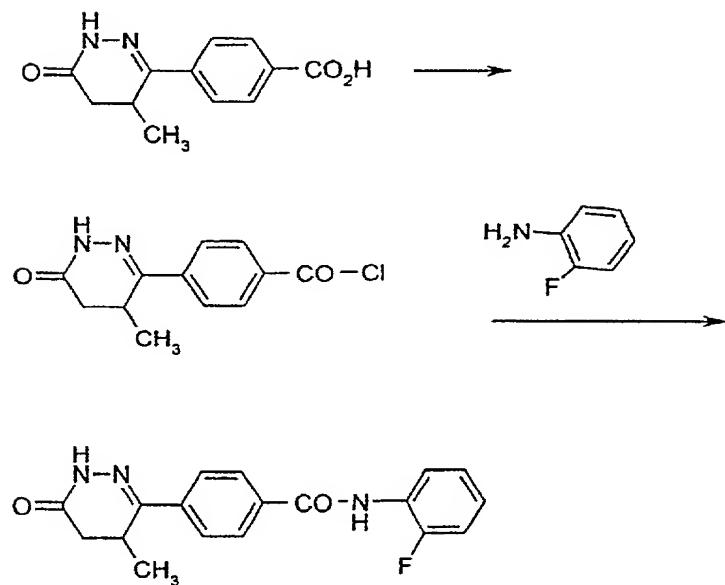
The methods according to the invention can be explained, by way of example, by means of the following formula schemes:

- 18 -

[A]

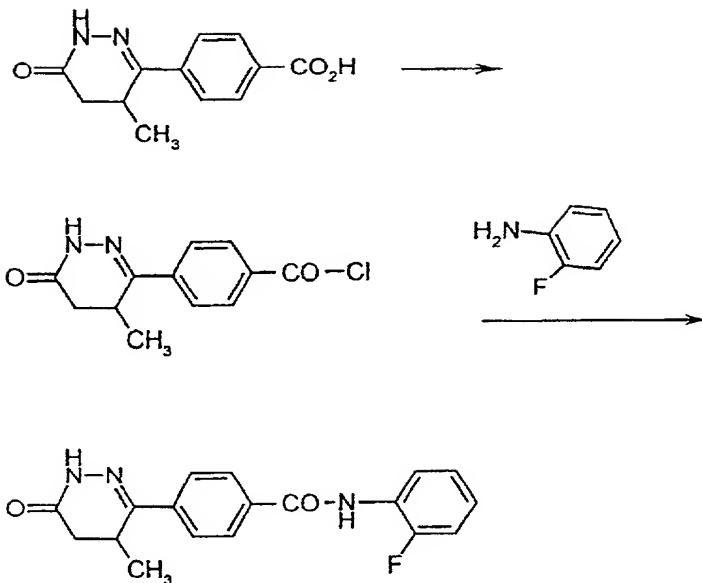


[B]



- 19 -

[B]



Suitable solvents in this connection are organic solvents which are inert under the reaction conditions. These include halogenohydrocarbons, such as dichloromethane,

- 5 trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, hydrocarbons, such as benzene, xylene, toluene, hexane or cyclohexane, ethers, such as diethyl ether, dioxane or THF, and also dimethylformamide, acetonitrile, acetone or hexamethylphosphoric triamide. Dichloromethane, DMF and dioxane are particularly preferable.
- 10 It is also possible to use solvent mixtures.

Suitable bases are the customary inorganic or organic bases. These preferably include alkali metal hydroxides, such as sodium or potassium hydroxide, or alkali metal carbonates, such as sodium or potassium carbonate, or sodium or potassium

- 15 methoxide or sodium or potassium ethoxide or potassium tert-butoxide or amides, such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or organometallic compounds, such as butyllithium or phenyllithium, and organic bases, such as triethylamide, pyridine, dimethylaminopyridine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBU) or N-methyl-
- 20 morpholine. Pyridine and triethylamine are preferred.

In this connection, the base can be employed in a quantity of from 1 to 5 mol, preferably of from 1 to 2 mol, based on 1 mol of the compounds of the general formula (II).

5

In general, the reaction takes place in a temperature range of from -78°C up to reflux temperature, preferably in the range from -78°C to +20°C.

The reaction can be carried out under normal, increased or decreased pressure (for example in the range from 0.5 to 5 bar). In general, the reaction is carried out under normal pressure.

The compounds of the general formulae (II), (III) and (V) are known per se or can be prepared using published methods [cf., with regard to compounds of the formula (II), J. Med. Chem. 17, (273-281), 1974].

Some of the compounds of the general formula (IV) are novel and can be prepared, for example, as described above.

The compounds of the general formula (I) according to the invention exhibit a valuable pharmacological spectrum of activity which was not foreseeable and are particularly suitable, therefore, for the prophylaxis and/or treatment of diseases.

They can preferably be employed in medicaments for the prophylaxis and/or treatment of anemias, such as in premature baby anemias, in nephrogenic or renal anemias, such as anemias associated with chronic renal insufficiency, in anemias following chemotherapy and in the anemia suffered by HIV patients, i.e. they can consequently be used, in particular, for treating severe anemias.

Even when the endogenous EPO production is completely intact, administration of the compounds according to the invention can induce an additional stimulation of

- 21 -

erythropoiesis, something which can be exploited, in particular, in the case of individuals donating their own blood.

All the customary administration forms are suitable for administering the compounds

5 according to the invention. The administration is preferably effected orally, transdermally or parenterally. Very particular preference is given to oral administration, which represents an additional advantage as compared with the therapy of anemias with rhEPO, as is known from the prior art.

10 The compounds according to the invention act, in particular, as erythropoietin sensitizers. "Erythropoietin sensitizers" is the term used for compounds which are able to influence the action of the EPO which is present in the body so efficiently that erythropoiesis is increased and, in particular, oxygen supply is improved. Surprisingly, the compounds are also active orally, thereby substantially improving
15 and simultaneously simplifying therapeutic use while excluding or reducing the known side-effects.

The present invention thus also relates to the use of the EPO sensitizers for stimulating erythropoiesis, in particular for the prophylaxis and/or treatment of

20 anemias, preferably severe anemias, such as premature baby anemia, anemia associated with chronic kidney insufficiency, anemia following chemotherapy or else anemia in HIV patients. Particular preference is given to administering the so-called EPO sensitizers orally for the abovementioned purposes.

25 Thus, the compounds according to the invention enable erythropoiesis to be stimulated efficiently and consequently make possible a prophylaxis and/or therapy of anemias which intervenes prior to the stage at which the conventional methods of treatment with EPO begin. This is because the compounds according to the invention enable the endogenous EPO to be influenced effectively, thereby making it possible
30 to avoid direct administration of EPO together with the disadvantages associated therewith.

- 22 -

The present invention consequently also relates to medicaments and pharmaceutical compositions which comprise at least one compound of the general formula (I) according to the invention together with one or more pharmacologically harmless auxiliary or carrier substances, and also to their use for stimulating erythropoiesis, in 5 particular for the purposes of prophylaxis and/or treatment of anemias, such as premature baby anemia, anemias associated with chronic renal insufficiency, anemias following chemotherapy or anemias in HIV patients.

The present invention will be illustrated by the following examples, which do not, 10 however, limit the invention in any way.

A Assessment of physiological efficacy

1. General test methods

15

a) Test description (in vitro)

Proliferation of human erythrocytic precursor cells

20 ml of heparinized blood were diluted with 20 ml of PBS (phosphate-buffer saline) and centrifuged for 20 min (220 × g). The supernatant was discarded and the cells 20 were resuspended in 30 ml of PBS and pipetted onto 17 ml of Ficoll Paque® (d = 1.077 g/ml, Pharmacia) in a 50 ml tube. The samples were centrifuged at 800 × g for 20 min. The mononuclear cells at the boundary layer were transferred into a new centrifuge tube, diluted with 3 times the volume of PBS and centrifuged at 300 × g for 5 min. The CD34-positive cells from this cell fraction were isolated using 25 a commercial purification method (CD34 Multisort Kit supplied by Miytenyi). The CD34-positive cells (6 000-10 000 cells/ml) were resuspended in stem cell medium (0.9% methyl cellulose, 30% calf serum, 1% albumin (bovine), 100 µM 2-mercaptoethanol and 2 mM L-glutamine) supplied by StemCell Technologies Inc. 10 mU of human erythropoietin/ml, 10 ng of human IL-3 (interleukin-3)/ml and 0-10 µM test 30 substance were added. 500 µl were cultured per well (microtiter plates in each case containing 24 wells) at 37°C for 14 days and in 5% CO₂/95% air.

- 23 -

The cultures were diluted with 20 ml of 0.9% w/v NaCl solution, centrifuged at 600 × g for 15 min and resuspended in 200 µl of 0.9% w/v NaCl. In order to determine the number of erythrocytic cells, 50 µl of the cell suspension were pipetted into 10 µl of benzidine staining solution (20 µg of benzidine in 500 µl of DMSO, 5 30 µl of H₂O₂ and 60 µl of concentrated acetic acid). The number of blue cells was counted with the aid of a microscope.

When the test substances according to the present invention are added, a significant increase in the proliferation of erythrocytic precursor cells is observed in each case.

10

b) Test description, mouse hematocrit

Normal mice are treated with test substances over several days. The test substances are administered intraperitoneally, subcutaneously or orally. Preferred solvents are Solutol/DMSO/sucrose/NaCl solution or Glycofurool.

15 From day 0 (prior to the first administration), up to approx. 3 days after the last administration, approx. 70 µl of blood are withdrawn on several occasions by puncturing the retroorbital venus plexus with a hematocrit capillary. The samples are centrifuged and the hematocrit is determined by reading off manually. The primary parameter is the increase in hematocrit, in relation to the starting value, in the treated animals as compared with the change in the hematocrit in the placebo control 20 (doubly standardized value).

The test substances according to the present invention which are administered lead to a significant increase in the hematocrit.

25

The novel active compounds can be converted, in a known manner, into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable carrier substances or solvents. In this connection, the therapeutically active compound should in each case be present at a concentration of from about 0.5 to 30 90% by weight of the total mixture, i.e. in quantities which are sufficient for achieving the given dosing latitude.

- 24 -

The formulations are prepared, for example, by extending the active compounds with solvents and/or carrier substances, where appropriate using emulsifying agents and/or dispersing agents, it being possible, for example when using water as a diluent, to use organic solvents as auxiliary solvents, where appropriate.

- 5 Administration is effected in a customary manner, preferably orally, transdermally or parenterally, in particular perlingually or intravenously.

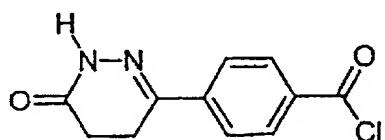
In general, it has proved to be advantageous, when administering intravenously, to administer quantities of from about 0.01 to 10 mg/kg, preferably of from about 0.1 to 10 mg/kg, of bodyweight in order to achieve effective results.

- 10 Despite this, it can be necessary, where appropriate, to diverge from the quantities mentioned, specifically in dependence on bodyweight or on the nature of the administration route, on the individual reaction to the drug, on the type of formulation and on the time or interval at which the administration takes place. Thus, it can be sufficient, in some cases, to make do with less than the previously
15 mentioned lowest quantity while, in other cases, it is necessary to exceed the abovementioned upper limit. When relatively large quantities are being administered, it can be advisable to divide these quantities into several single doses which are then given during the course of the day.

20 B Preparation examples

Example I: Preparing the starting compound

4-(1,4,5,6-Tetrahydro-6-oxo-3-pyridazinyl)benzoyl chloride



25

10 mmol (2.2 g) of 4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoic acid are suspended in 50 ml of dichloromethane, after which 1.5 ml (20 mmol) of thionyl chloride are added and the mixture is stirred for 24 hours while being boiled gently.

- 25 -

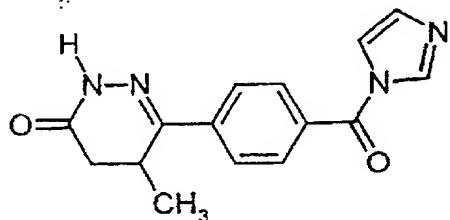
The mixture is then cooled down, separated off from insoluble material by being filtered with suction, and inspissated thoroughly. The inspissation residue is stirred up with toluene and filtered off with suction.

This results in 2.0 g of a crude product which is subjected to further reaction without

5 being purified.

Example II: Preparing the starting compound

4-(4-Methyl-1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoic imidazolide



10

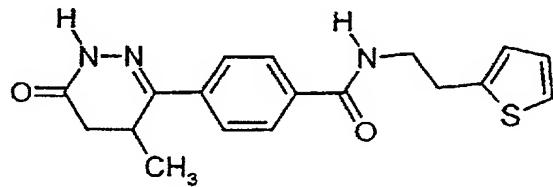
4.7 g (20.24 mmol) of 4-(4-methyl-1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoic acid are suspended in 120 ml of THF (anhydrous), after which 3.97 g (24.50 mmol)

of carbonyldiimidazole are added. This results in a solution from which an oily mass

15 separates out. The mixture is filtered and the filtrate is stirred for a further 3 hours. It is then inspissated, after which the residue is stirred up with a little THF; the solid is then filtered off with suction and washed with THF. This results in 3.9 g of virtually colorless crystals having a melting point of 171-174°C.

20 **Example 1**

4-(4-Methyl-1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoic 2-(2-thienylethyl)amide

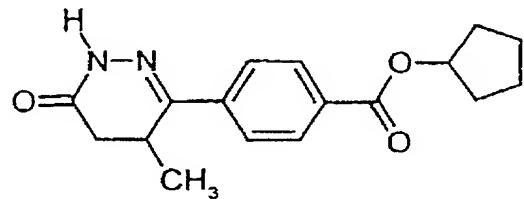


- 26 -

282 mg (1 mmol) of 4-(4-methyl-1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoic imidazolide from example II are stirred, at 100°C for 5 hours, in 3 ml of dioxane together with 254 mg (2 mmol) of 2-thienylethylamine. Cooling takes place followed by dissolution in dichloromethane; this solution is then washed twice with 1N hydrochloric acid, with water, with sodium hydrogen carbonate solution and once again with water, and then dried and inspissated. The inspissation residue is crystallized using ethyl acetate. This results in 218 mg (63.8% of theory) of colorless crystals having a melting point of 163-164°C.

10 **Example 2**

Cyclopentyl 4-(4-methyl-1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoate

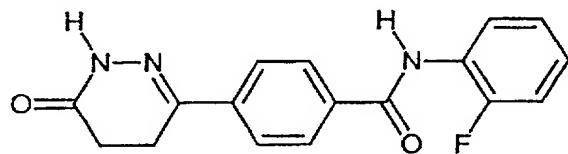


15 200 mg (0.71 mmol) of 4-(4-methyl-1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoic imidazolide from example II are stirred, at 100°C for 24 hours, in 2 ml of dioxane together with 2 ml of cyclopentanol. The mixture is inspissated as far as possible and separated on a column. The clean fractions crystallize using ether/heptane. This results in 53 mg of colorless crystals having a melting point of 120-122°C.

20

Example 3

6-[4-(2-Fluorophenylaminocarbonyl)phenyl]-4,5-dihydro-3(2H)-pyridazinone



25

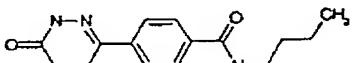
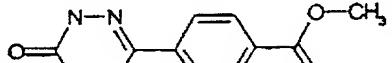
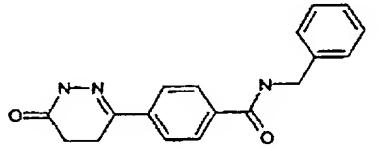
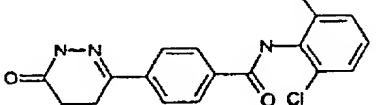
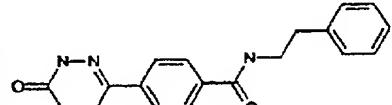
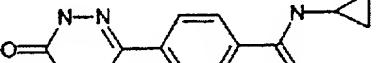
- 27 -

120 mg (0.5 mmol) of 4-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)benzoyl chloride from example I are stirred, at 60°C for 2 hours, in 5 ml of THF together with 56 mg (0.5 mmol) of 2-fluoroaniline and 0.1 ml of pyridine. The mixture is cooled down and inspissated. The inspissation residue is purified on a silica gel column. The clean 5 fractions are combined, inspissated, crystallized using methanol, filtered-off with suction and washed with methanol. This results in 60 mg of colorless crystals having a melting point of 242-244°C.

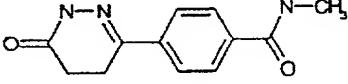
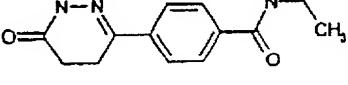
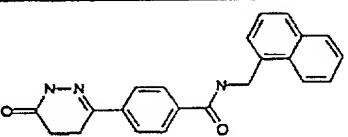
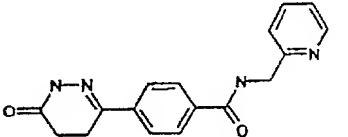
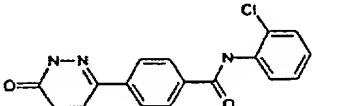
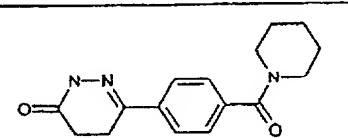
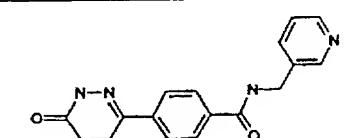
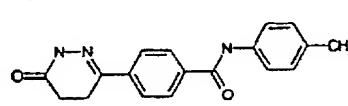
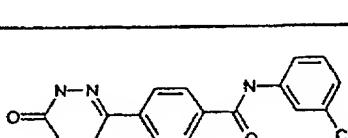
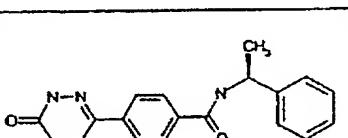
The substances listed in the following table are prepared in analogy with the above-
10 mentioned directions given in examples 1 to 3. In the case of the structures in the
following table which contain the  radical(s), it is always a  function which is meant.

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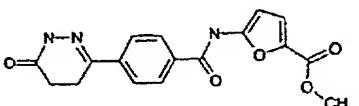
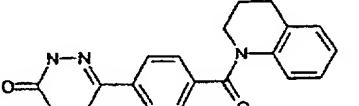
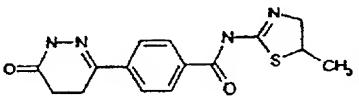
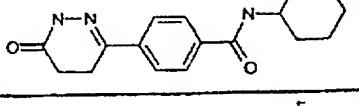
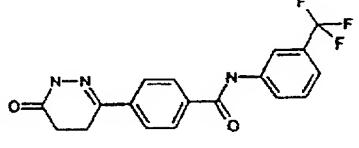
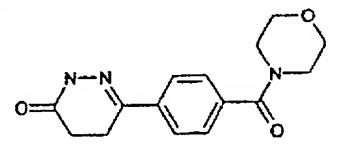
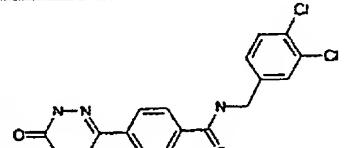
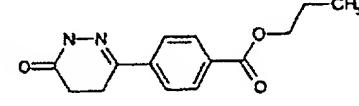
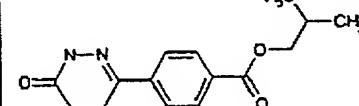
- 28 -

Ex. No.	Structure	MW	m.p.:
4		273.34	217-218
5		297.32	208-210
6		232.24	203-205
7		307.36	208-209
8		362.22	>250
9		260.30	155-156
10		321.38	223-226
11		257.29	248-50
12		246.27	157-159
13		293.33	>250

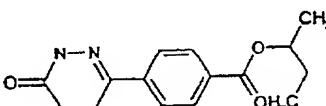
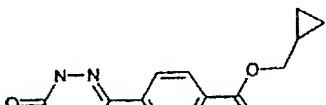
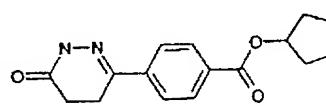
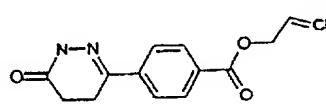
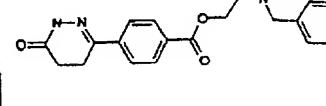
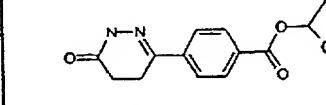
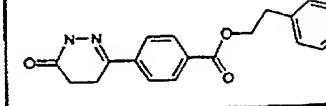
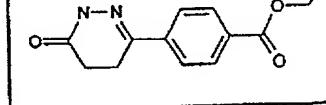
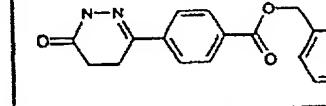
- 29 -

Ex. No.	Structure	MW	m.p.:
14		231.26	233-234
15		245.28	228-230
16		357.42	258-260
17		308.34	228-230
18		327.77	209-210
19		285.35	182-184
20		308.34	220-223
21		307.36	>250
22		327.77	>250
23		321.38	242-243

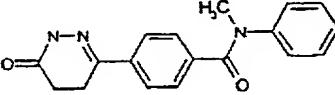
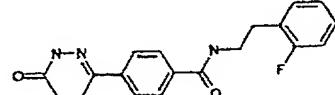
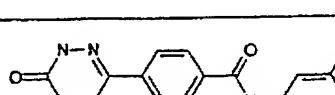
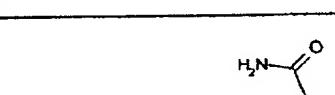
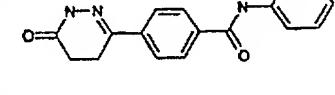
- 30 -

Ex. No.	Structure	MW	m.p.:
24		341.33	>260
25		333.39	215-216
26		316.38	>260
27		299.38	249-250
28		361.33	229-230
29		287.32	202-203
30		376.25	208-209
31		260.30	283-284
32		274.32	259-260

- 31 -

Ex. No.	Structure	MW	m.p.:
33		274.32	120-122
34		272.31	158-159
35		286.33	167-169
36		258.28	131-133
37		365.44	90-91
38		286.33	104-105
39		322.37	146-148
40		286.33	155-156
41		308.34	156-157

- 32 -

Ex. No.	Structure	MW	m.p.:
42		307.36	208-209
43		339.37	189-190
44		327.41	215-216
45		329.31	278-279
46		311.32	260 Z
47		342.38	>250
48		336.35	283 Z
49		325.35	186-7
50		316.38	>260

- 33 -

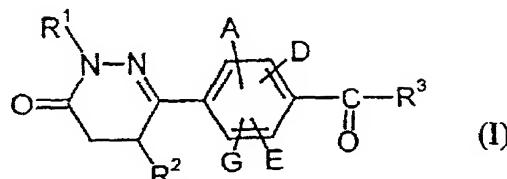
Ex. No.	Structure	MW	m.p.:
51		336.35	>250
52		342.38	>250
53		308.00	267-268
54		357.00	266-267
55		357.00	271-272
56		347.00	>260
57		271.00	216-217
58		301.00	152-153

- 34 -

Ex. No.	Structure	MW	m.p.:
59		411.00	186-187
60		365.00	245-246
61		365.00	164-165
62		287.00	166-167
63		395.00	146-147

Patent claims

1. A 6-carboxyphenyldihydropyridazinone derivative of the general formula (I)



5

in which

A, D, E and G are identical or different and

10 represent hydrogen, halogen, trifluoromethyl or hydroxyl, or represent (C₁-C₆)-alkyl or represent (C₁-C₆)-alkoxy,

R¹ and R² are identical or different and

represent hydrogen or represent (C₁-C₆)-alkyl,

15

R³ represents radicals of the formulae -OR⁴ or -NR⁵R⁶,

in which

20

R⁴ denotes cycloalkyl having from 3 to 8 carbon atoms or (C₁-C₈)-alkyl which is optionally substituted by hydroxyl, (C₁-C₆)-alkoxy, cycloalkyl having from 3 to 8 carbon atoms or aryl having from 6 to 10 carbon atoms which, for its part, can be substituted, once to twice, identically or differently, by substituents which are selected from the group: halogen, (C₁-C₆)-alkoxy, hydroxyl or trifluoromethyl, or denotes (C₁-C₈)-alkyl which is optionally substituted by a group of the formula -NR⁷R⁸,

25

in which

R⁷ and R⁸ are identical or different and denote hydrogen, (C₁-C₆)-alkyl or benzyl,
5

or

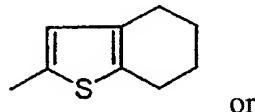
R⁴ denotes vinyl or allyl,
10

or

R⁴ denotes aryl having from 6 to 10 carbon atoms which is optionally substituted, once to twice, identically or differently, by substituents which are selected from the group consisting of: halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy or hydroxyl,
15

R⁵ denotes hydrogen or (C₁-C₄)-alkyl,
20

R⁶ denotes cycloalkyl having from 3 to 8 carbon atoms or a radical of the formula
25



aryl having from 6 to 10 carbon atoms or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the series S, N and/or O, it being possible for the ring systems which are listed here to be optionally substituted, once to several times, identically or differently, by substituents which are selected from the group: halogen, trifluoromethyl, hydroxyl, (C₁-C₆)-alkoxy, carboxyl, (C₁-C₆)-alkoxycarbonyl,

- 37 -

(C₁-C₆)-alkyl and radicals of the formulae -SO₂-NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

in which

5

R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or (C₁-C₆)-alkyl,

and

10

a denotes a number 0 or 1,

or

15

R⁶ denotes (C₁-C₈)-alkyl which is optionally substituted, once to twice, identically or differently, by substituents which are selected from the group: halogen, trifluoromethyl, hydroxyl, (C₁-C₆)-alkoxy, carboxyl, (C₁-C₆)-alkoxycarbonyl and aryl having from 6 to 10 carbon atoms and a 5- to 7-membered aromatic heterocycles having up to 3 heteroatoms from the series S, N and/or O, in which the ring systems can be optionally substituted, once to three times, identically or differently, by (C₁-C₆)-alkyl, halogen, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, trifluoromethyl or by the radical -CO-NH₂,

20

or

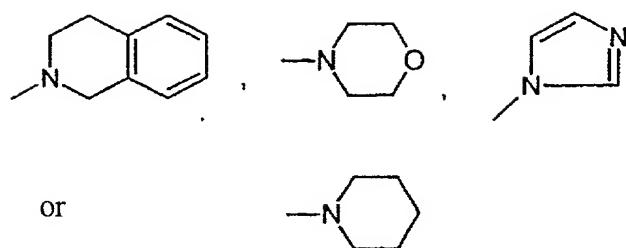
25

or

30

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae

- 38 -



which, for their part, can be optionally substituted,

5 and the salts thereof,

with the exception, however, of the compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide.

10 2. A 6-carboxyphenyldihydropyridazinone derivative of the general formula (I)
as claimed in claim 1,

in which

15 A, D, E and G are identical or different and
represent hydrogen, fluorine, chlorine, bromine or trifluoromethyl,

R^1 and R^2 are identical or different and
represent hydrogen or represent methyl,

20 R^3 represents radicals of the formulae $-OR^4$ or $-NR^5R^6$,

in which

25 R^4 denotes cyclopropyl, cyclopentyl or cyclohexyl or
denotes (C_1-C_6)-alkyl which is optionally substituted by
hydroxyl, (C_1-C_4)-alkoxy, cyclopropyl, cyclopentyl,

- 39 -

cyclohexyl or phenyl which, for its part, can be substituted once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, (C₁-C₄)-alkoxy, hydroxyl or trifluoromethyl, or

5

denotes (C₁-C₆)-alkyl which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

10

R⁷ and R⁸ are identical or different and denote hydrogen or (C₁-C₄)-alkyl,

or

15

R⁴ denotes allyl,

R⁵ denotes hydrogen or (C₁-C₃)-alkyl,

20

R⁶ denotes cyclopropyl, cyclopentyl or cyclohexyl or denotes phenyl, thienyl, thiazolyl, furyl or pyridyl, it being possible for the listed aromatic ring systems to be optionally substituted, once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl, (C₁-C₄)-alkyl and radicals of the formulae -SO₂NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

25

in which

30

R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or (C₁-C₄)-alkyl,

- 40 -

and

a denotes a number 0 or 1,

5

or

R⁶ denotes (C₁-C₆)-alkyl which are optionally substituted once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkoxycarbonyl, phenyl, pyridyl, naphthyl, furyl or thiazolyl, it being possible for the ring systems to be optionally substituted, once to twice, identically or differently, by fluorine, chlorine, methyl, methoxycarbonyl, trifluoromethyl or by a radical of the formula -CO-NH₂,

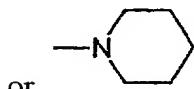
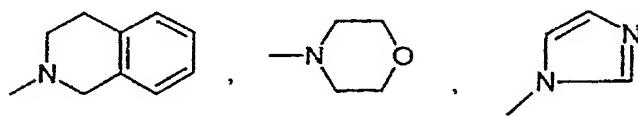
10

15

or

20

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae



or

25

and the salts thereof,

- 41 -

with the exception, however, of the compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide.

3. A 6-carboxyphenyldihydropyridazinone derivative of the general formula (I)
5 as claimed in claim 1,

in which

A, D, E and G represent hydrogen,

10 R¹ and R² are identical or different and
represent hydrogen or represent methyl,

15 R³ represents radicals of the formulae -OR⁴ or -NR⁵R⁶,

in which

20 R⁴ denotes cyclopropyl, cyclopentyl or cyclohexyl or
denotes (C₁-C₅)-alkyl which is optionally substituted by
(C₁-C₄)-alkoxy, cyclopropyl, cyclopentyl, cyclohexyl or
phenyl which, for its part, can be substituted, once to twice,
identically or differently, by substituents selected from the
group: fluorine, chlorine, (C₁-C₄)-alkoxy, hydroxyl or
trifluoromethyl, or

25 denotes (C₁-C₄)-alkyl which is optionally substituted by a
group of the formula -NR⁷R⁸,

in which

30 R⁷ and R⁸ are identical or different and denote hydrogen, benzyl or
methyl,

- 42 -

or

5 R⁴ denotes allyl,

10 R⁵ denotes hydrogen or (C₁-C₃)-alkyl,

15 R⁶ denotes cyclopropyl, cyclopentyl or cyclohexyl or
 denotes naphthyl, phenyl, thienyl, thiazolyl, furyl or pyridyl,
 the listed ring systems being optionally substituted once to
 twice, identically or differently, by substituents selected from
 the group: fluorine, chlorine, bromine, trifluoromethyl,
 (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl, (C₁-C₃)-alkyl and
 radicals of the formulae -SO₂-NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

20 in which

25 R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or
 (C₁-C₄)-alkyl,

20 and

25 a denotes a number 0 or 1,

or

30 R⁶ denotes (C₁-C₆)-alkyl which is optionally substituted by
 substituents selected from the group: fluorine, chlorine,
 trifluoromethyl, (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl,
 phenyl, pyridyl, naphthyl, furyl, thienyl or thiazolyl, the ring
 systems optionally being substituted once to twice, identically

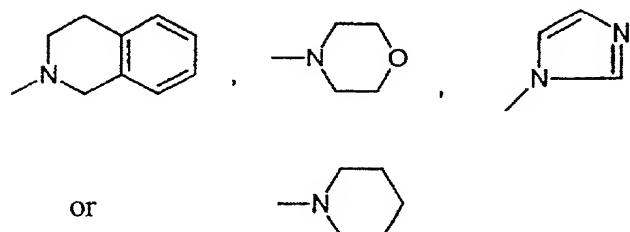
- 43 -

or differently, by fluorine, chlorine, methyl, methoxycarbonyl or trifluoromethyl or by a radical of the formula -CO-NH₂,

or

5

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae



or

10

and the salts thereof,

with the exception, however, of the compound N-methyl-4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)benzamide.

15

4. A 6-carboxyphenyldihydropyridazinone derivative of the general formula (I) as claimed in claim 1,

in which

20

A, D, E and G represent hydrogen,

R³ represents the radical -NR⁵R⁶, where R⁵ = H or methyl and R⁶ is as previously defined,

25

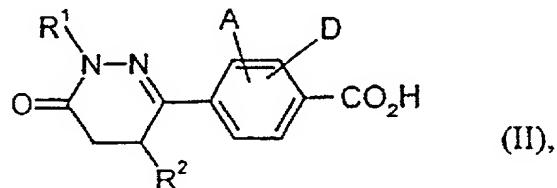
and the remaining radicals have the previously mentioned meaning.

- 44 -

5. A process for preparing 6-carboxy-phenyl-dihydropyridazinone derivatives as claimed in claims 1 to 4, characterized in that

5 [A] in the case where R³ represents the radical of the formula -OR⁴ in the above general formula (I),

compounds of the general formula (II)



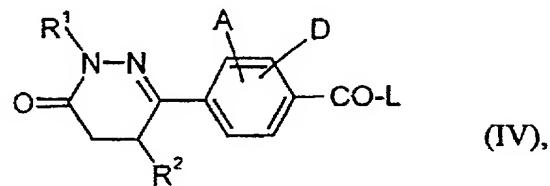
10

in which

A, D, R¹ and R² have the abovementioned meaning,

15

are initially converted, by reaction with carboxylic acid-activating reagents, using customary methods, into the compounds of the general formula (IV)



20

in which

A, D, R¹ and R² have the abovementioned meaning,

and

- 45 -

L represents an activating radical, preferably chlorine or imidazolyl,
and, in a second step, reacted with compounds of the general formula
5 (III)



in which

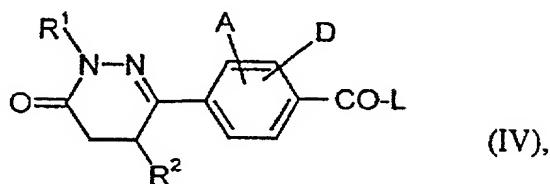
10 R⁴ has the abovementioned meaning,

15 in inert solvents, where appropriate in the presence of a base,

or

[B] in the case where R³ represents the radical of the formula -NR⁵R⁶ in
the above general formula (I),

20 compounds of the general formula (II) are initially converted, by reaction
with carboxylic acid-activating reagents, and using customary methods, into
the compounds of the general formula (IV)



25 in which

A, D, R¹ and R² have the abovementioned meaning,

and

L represents an activating radical, preferably chlorine or imidazolyl,

5

and, in a second step, reacted with amides of the general formula (V)

HNR^5R^6 (V),

10 in which

R^5 and R^6 have the abovementioned meaning,

15 in inert solvents.

15

6. A medicament or pharmaceutical composition which comprises at least one compound as claimed in claims 1 to 4 and also one or more pharmaco- logically harmless auxiliary and carrier substances.

20 7. A medicament or pharmaceutical composition as claimed in claim 6 for the prophylaxis and/or treatment of anemias.

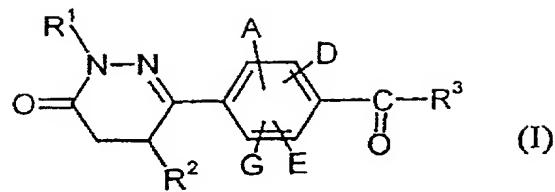
8. A medicament or pharmaceutical composition as claimed in claim 6 or 7 for treating premature baby anemias, anemias associated with chronic renal insufficiency, anemias following chemotherapy and anemias in HIV patients.

25

9. A medicament or pharmaceutical composition as claimed in claim 6 for stimulating the erythropoiesis of individuals donating their own blood.

30 10. The use of 6-carboxyphenyldihydropyridazinone derivatives of the general formula (I)

- 47 -



in which

- 5 A, D, E and G are identical or different and
represent hydrogen, halogen, trifluoromethyl or hydroxyl, or represent
(C₁-C₆)-alkyl or represent (C₁-C₆)-alkoxy,
- 10 R¹ and R² are identical or different and
represent hydrogen or represent (C₁-C₆)-alkyl,
- 15 R³ represents radicals of the formulae -OR⁴ or -NR⁵R⁶,
in which
R⁴ denotes cycloalkyl having from 3 to 8 carbon atoms or
(C₁-C₈)-alkyl which is optionally substituted by hydroxyl,
(C₁-C₆)-alkoxy, cycloalkyl having from 3 to 8 carbon atoms or
aryl having from 6 to 10 carbon atoms which, for its part, can
be substituted, once to twice, identically or differently, by
substituents which are selected from the group: halogen,
20 (C₁-C₆)-alkoxy, hydroxyl or trifluoromethyl, or
denotes (C₁-C₈)-alkyl which is optionally substituted by a
25 group of the formula -NR⁷R⁸,

in which

- 48 -

R^7 and R^8 are identical or different and denote hydrogen, (C_1-C_6)-alkyl or benzyl,

or

5

R^4 denotes vinyl or allyl,

or

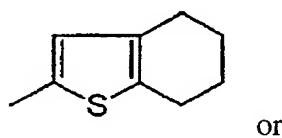
10

R^4 denotes aryl having from 6 to 10 carbon atoms which is optionally substituted, once to twice, identically or differently, by substituents which are selected from the group consisting of: halogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or hydroxyl,

15

R^5 denotes hydrogen or (C_1-C_4)-alkyl,

R^6 denotes cycloalkyl having from 3 to 8 carbon atoms or a radical of the formula



or

20

aryl having from 6 to 10 carbon atoms or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the series S, N and/or O, it being possible for the ring systems which are listed here to be optionally substituted, once to several times, identically or differently, by substituents which are selected from the group: halogen, trifluoromethyl,

25

hydroxyl, (C_1-C_6)-alkoxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkyl and radicals of the formulae $-SO_2-NR^9R^{10}$ and $-(CO)_a-NR^{11}R^{12}$,

30

in which

- 49 -

R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or (C₁-C₆)-alkyl,

5 and

a denotes a number 0 or 1,

or

10

R⁶ denotes (C₁-C₈)-alkyl which is optionally substituted, once to twice, identically or differently, by substituents which are selected from the group: halogen, trifluoromethyl, hydroxyl, (C₁-C₆)-alkoxy, carboxyl, (C₁-C₆)-alkoxycarbonyl and aryl having from 6 to 10 carbon atoms and a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the series S, N and/or O, in which the ring systems can be optionally substituted, once to three times, identically or differently, by (C₁-C₆)-alkyl, halogen, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxycarbonyl, trifluoromethyl or by the radical -CO-NH₂,

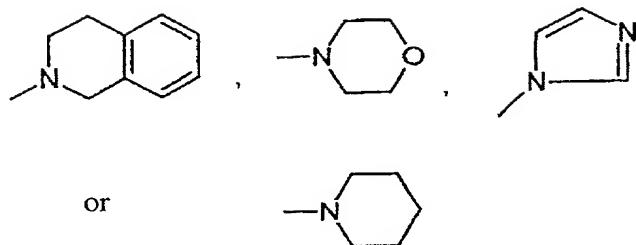
15

or

20

25 R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae

- 50 -



which, for their part, can be optionally substituted,

5 and the salts thereof,

for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of anemias.

10 11. The use of 6-carboxyphenyldihydropyridazinone derivatives of the general formula (I) as claimed in claim 10,

in which

15 A, D, E and G are identical or different and
represent hydrogen, fluorine, chlorine, bromine or trifluoromethyl,

R¹ and R² are identical or different and
represent hydrogen or represent methyl,

20 R³ represents radicals of the formulae -OR⁴ or -NR⁵R⁶,

in which

25 R⁴ denotes cyclopropyl, cyclopentyl or cyclohexyl or
denotes (C₁-C₆)-alkyl which is optionally substituted by
hydroxyl, (C₁-C₄)-alkoxy, cyclopropyl, cyclopentyl,

- 51 -

or phenyl which, for its part, can be substituted once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, (C₁-C₄)-alkoxy, hydroxyl or trifluoromethyl, or

5

denotes (C₁-C₆)-alkyl which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

10

R⁷ and R⁸ are identical or different and denote hydrogen or (C₁-C₄)-alkyl,

or

15

R⁴ denotes vinyl or allyl,

R⁵ denotes hydrogen or (C₁-C₃)-alkyl,

20

R⁶ denotes cyclopropyl, cyclopentyl or cyclohexyl or denotes phenyl, thienyl, thiazolyl, furyl or pyridyl, it being possible for the listed aromatic ring systems to be optionally substituted, once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl, (C₁-C₄)-alkyl and radicals of the formulae -SO₂NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

in which

25

R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or (C₁-C₄)-alkyl,

- 52 -

and

a denotes a number 0 or 1,

5

or

10

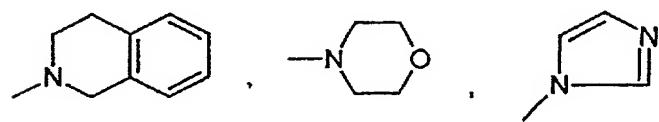
R⁶ denotes (C₁-C₆)-alkyl which are optionally substituted once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, (C₁-C₄)-alkoxy, (C₁-C₄)-alkoxycarbonyl, phenyl, pyridyl, naphthyl, furyl or thiazolyl, it being possible for the ring systems to be optionally substituted, once to twice, identically or differently, by fluorine, chlorine, methyl, methoxycarbonyl, trifluoromethyl or by a radical of the formula -CO-NH₂,

15

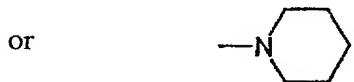
or

20

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae



or



25

which are in turn optionally substituted,

and the salts thereof,

- 53 -

for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of anemias.

- 5 12. The use of 6-carboxyphenyldihydropyridazinone derivatives of the general formula (I) as claimed in claim 10,

in which

10 A, D, E and G represent hydrogen,

R¹ and R² are identical or different and
represent hydrogen or represent methyl,

15 R³ represents radicals of the formulae -OR⁴ or -NR⁵R⁶,

in which

20 R⁴ denotes cyclopropyl, cyclopentyl or cyclohexyl or
denotes (C₁-C₅)-alkyl which is optionally substituted by
(C₁-C₄)-alkoxy, cyclopropyl, cyclopentyl, cyclohexyl or
phenyl which, for its part, can be substituted, once to twice,
identically or differently, by substituents selected from the
group: fluorine, chlorine, (C₁-C₄)-alkoxy, hydroxyl or
25 trifluoromethyl, or

denotes (C₁-C₄)-alkyl which is optionally substituted by a
group of the formula -NR⁷R⁸,

30 in which

- 54 -

R⁷ and R⁸ are identical or different and denote hydrogen, benzyl or methyl,

or

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R⁴ denotes allyl,

R⁵ denotes hydrogen or (C₁-C₃)-alkyl,

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R⁶ denotes cyclopropyl, cyclopentyl or cyclohexyl or denotes naphthyl, phenyl, thienyl, thiazolyl, furyl or pyridyl, the listed ring systems being optionally substituted once to twice, identically or differently, by substituents selected from the group: fluorine, chlorine, bromine, trifluoromethyl, (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl, (C₁-C₃)-alkyl and radicals of the formulae -SO₂-NR⁹R¹⁰ and -(CO)_a-NR¹¹R¹²,

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in which

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R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen or (C₁-C₄)-alkyl,

and

25

a denotes a number 0 or 1,

or

30

R⁶ denotes (C₁-C₆)-alkyl which is optionally substituted by substituents selected from the group: fluorine, chlorine, trifluoromethyl, (C₁-C₃)-alkoxy, (C₁-C₃)-alkoxycarbonyl, phenyl, pyridyl, naphthyl, furyl, thienyl or thiazolyl, the ring

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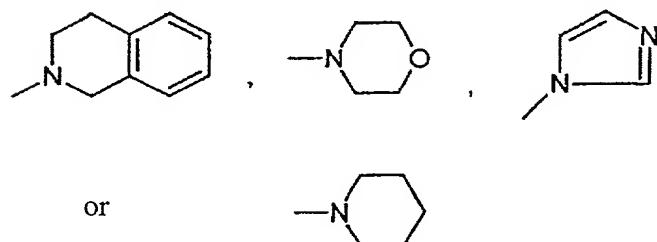
ring systems optionally being substituted once to twice, identically or differently, by fluorine, chlorine, methyl, methoxycarbonyl or trifluoromethyl or by a radical of the formula -CO-NH₂,

5

or

R⁵ and R⁶ form, together with the nitrogen atom, cyclic radicals of the formulae

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which are in turn optionally substituted,

15

and the salts thereof,

for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of anemias.

20

13. The use of 6-carboxyphenyldihydropyridazinone derivatives of the general formula (I) as claimed in claim 10,

in which

25

A, D, E and G represent hydrogen,

- 56 -

R³ represents the radical -NR⁵R⁶, where R⁵ = H or methyl and R⁶ is as previously defined,

and the remaining radicals have the previously given meaning,

5

and the salts thereof,

for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of anemias.

10

14. The use as claimed in one of claims 10 to 13 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of premature baby anemias, anemias associated with chronic renal insufficiency, anemias following chemotherapy and anemias in HIV patients.

15

15. The use as claimed in one of claims 10 to 13 for preparing medicaments or pharmaceutical compositions for stimulating the erythropoiesis of individuals donating their own blood.

20

16. The use of erythropoietin sensitizers for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of anemias.

25

17. The use as claimed in claim 16 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of premature baby anemias, anemias associated with chronic renal insufficiency, anemias following chemotherapy and anemias in HIV patients.

30

18. The use of erythropoietin sensitizers for preparing medicaments or pharmaceutical compositions for stimulating the erythropoiesis of individuals donating their own blood.

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19. The use as claimed in one of claims 16 to 18, characterized in that the erythropoietin sensitizers are administered orally.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
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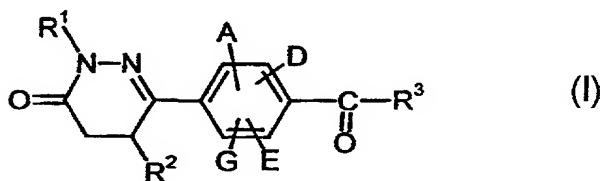
Veröffentlicht:

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- Vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen.

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: 6-CARBOXYPHENYLDIHYDROPYRIDAZINONE DERIVATIVES AND USE THEREOF

(54) Bezeichnung: 6-CARBOXYPHENYLDIHYDROPYRIDAZINON-DERIVATE UND IHRE VERWENDUNG



(57) Abstract: The invention relates to the area of erythropoiesis, in particular to substituted 6-carboxyphenyldihydropyridazinone derivatives of general formula (I), to methods for producing them and to their use as medicaments, preferably for preventing and/or treating anaemia.

WO 01/00589 A1

(57) Zusammenfassung: Die Erfindung betrifft das Gebiet der Erythropoese. Insbesondere werden substituierte 6-Carboxyphenyldihydropyridazinon-Derivate der allgemeinen Formel (I), Verfahren zu ihrer Herstellung und ihre Verwendung als Arzneimittel, vorzugsweise zur Prophylaxe und/oder Bekämpfung von Anämien, beschrieben.

10 APR 2000

COMBINED DECLARATION AND POWER OF ATTORNEY	ATTORNEY DOCKET NO
	Le A 33 783

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought
on the invention entitled

6-CARBOXYPHENYLDIHYDROPYRIDAZINONE DERIVATIVES AND USE THEREOF

the specification of which is attached hereto,

or was filed on June 16, 2000

as a PCT Application Serial No. PCT/EP00/05564

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

199 29 782.7 (Number)	Germany (Country)	June 29, 1999 (Month/Day/Year Filed)
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I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

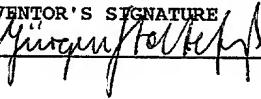
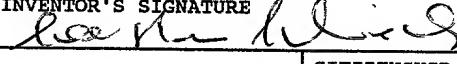
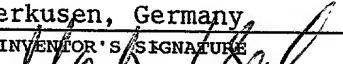
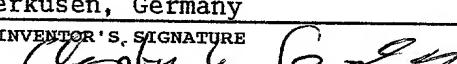
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Le A 33 783-US

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RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FOURTEENTH INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FIFTEENTH INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SIXTEENTH INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SEVENTEENTH INVENTOR	INVENTOR'S SIGNATURE	DATE
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POST OFFICE ADDRESS		